REMARKS

Claims 63-78, 88-122, 128-145, and 147-161 are pending in the application. Claims 70-78, 96-107, 115-118, 139-145, and 151-155, are withdrawn from examination as directed to a non-elected invention. Claims 68, 69, 88, 90-92, 108-114, 119, 137, 138, 147, 149, 156-159, and 161 are withdrawn from examination as directed to a non-elected species. Claims 63-67, 89, 93-95, 120-122, 128-136, 148, 150, and 160 are under examination on the merits to the extent that they read on the elected species, designated as recombinant RSV with a SH gene or genome segment deletion. With entry of this amendment, claims 122, 128, 129, 130, and 131 have been amended and claim 120 canceled for clarity in accordance with the Office's suggestions. The subject amendments are fully supported by the disclosure and no new matter has been added to the application.

Information Disclosure Statement

The Office acknowledges receipt of the Information Disclosure Statements filed on July 7, 2000 (Paper No. 7) and December 8, 2000 (Paper NO. 11). However, the Office has not yet considered at least the references set forth in Paper No. 7 (see Office Action Paper No. 17 at p. 2), because the parent file containing the references reportedly remains unavailable. Applicants respectfully request that the Office seek once more to determine the availability of the subject references from the parent file. Alternatively, Applicants invite the Examiner to call Applicants' representative at the number identified below to clarify which references may need to be resubmitted by Applicants (i.e., from one or both of IDS submissions Papers No. 7 and 11).

Double Patenting

Claim 131 stands provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 23, 24, and 62 of copending Application No. 09/291,894. The Office contends that, although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are drawn to recombinant RSV

comprising RSV with sequences of different subgroups (A and B) and an SH gene deletion.

Applicants note that this is a provisional obviousness-type double patenting rejection, and respectfully defer their response to the merits of the rejection until the allegedly conflicting claim(s) in one of the subject cases is/are allowed.

Claim Objections

Applicants acknowledge that the Office has reconsidered and withdrawn the prior objection to claim 120 under 37 CFR 1.75(c).

Patentability Under 35 U.S.C. § 112, First Paragraph

Claims 128-131 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Office focused on specific language of the claims reciting a "vaccine to induce protection against RSV" and challenged that such specific efficacy of the subject compositions is allegedly not enabled.

Applicants respectfully traverse the stated grounds for rejection and submit that the specification fully enables production of live-attenuated RSV vaccines capable of eliciting a protective immune response in human subjects. In this regard, Applicants rely on the detailed facts and remarks presented in their prior Amendment/Response filed November 9, 2001 and subsequent Communication filed February 28, 2002, each incorporated herein by reference.

The instant rejection, however, is obviated by Applicants' clarifying amendments to the claims herein. The claims no longer specifically recite a "vaccine" composition that is necessarily effective "to induce protection against RSV." Rather, the amended claims recite "[a]n immunogenic composition effective to elicit an immune response in a mammalian subject directed against RSV." Thus, the amended claims embrace compositions having a variety of corresponding uses, including for example laboratory and clinical diagnostic uses, screening uses, and various immunization methods, including human vaccine uses.

To evaluate enablement of these amended claims, the Office's attention is respectfully directed to the Training Materials for Examining Patent Applications With

Respect to 35 U.S.C. Section 112, First Paragraph-Enablement Chemical/Biotechnical Applications (hereinafter "Enablement Guidelines"), at Section Sec. III(A)(2)):

> [W]hen a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention (emphasis supplied).

In the instant case, the claims no longer recite a specific use limitation for the claimed compositions as a "protective" "vaccine", and the subject compositions are clearly enabled for a number of different uses commensurate with the claims presented for review. Accordingly, withdrawal of the rejection of claims 128-131 under 35 U.S.C. § 112, first paragraph, is earnestly solicited.

Patentability Under 35 U.S.C. § 103

Claims 63-67, 89, 93-95, 120, 121, 128, 131-136, and 150 are rejected under 35 U.S.C. § 103 as allegedly obvious over Collins et al. (Proc. Natl. Acad. Sci. USA 92:11563-11567, 1995). Previously, the Office stated that Collins et al. teach "infectious recombinant RSV . . . wherein defined changes can be introduced for development of live attenuated vaccine strains" (Office Action Paper No. 15, at p. 8). In addition, the Office formerly argued that Collins and coworkers suggest that deletion or modification of specific genes, particularly including the SH gene, "may result in attenuated RSV strains with enhanced immunogenicity and a higher level of protection against RSV infection than wild-type virus." (id., emphasis supplied)

Thus, the initial position advocated by the Office was that Collins et al. actually disclosed RSV having defined changes for use in a live attenuated vaccine, and that the reference further suggested that a recombinant RSV having a partial or complete gene deletion could be made with an expectation of achieving such desired characteristics

as attenuation, enhanced immunogenicity, and a higher level of protection.

This initial characterization presented by the Office concerning the teachings of Collins et al. appears to now be withdrawn. In the current Office Action, the Examiner seems to propose that, even if no practical results were reasonably expected based on the Collins et al. teachings, the reference would still render claims to a recombinant RSV having a partial or complete gene deletion (as exemplified by an SH gene deletion) obvious (Office Action Paper No. 17, at pp. 4-5). This redacted view clearly contravenes governing legal authority.

Long established case law makes it clear that a reference relied upon under 35 U.S.C. § 103 must provide a practical motivation to make a claimed invention, which generally requires a reasonable expectation of success that the invention will yield the "particular results" disclosed in an Applicants' specification. Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143, 227 U.S.P.Q.d 543 (Fed. Cir. 1985). The Feil court explained this test as requiring a suggestion that a particular combination "could achieve the advantages of (the claimed invention)."

The particular results that support a suggestion or motivation to make a claimed invention must be provided by the cited reference, but they need not be specifically recited in the claims under review, contrary to the Office's assertion (see Paper No. 17, at pp. 54). This is clear from the Federal Circuit's reasoning in In re Dow Chemical Co., 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529 (1988):

> There must be a reason or suggestion in the art for selecting the (combination), other than the knowledge learned from the applicant's disclosure.

To determine whether a reference provides a reasonable expectation of success for achieving the desired results of a particular invention, the Federal Circuit's predecessor court stated in In re Gyurik, 201 USPQ 552, 557 (CCPA 1979) as follows:

> An element in determining obviousness of a new chemical compound is the motivation of one having ordinary skill in the art to make it. That motivation is not abstract, but practical, and is always related to the properties or uses one skilled in the art would expect the compound to have, if made.

Thus, a reliable reference under 35 U.S.C. § 103 must not only suggest the

claimed compound or composition (e.g., a recombinant RSV having a partial or complete gene deletion), but must also reasonably forecast the properties that the skilled artisan would expect this new compound or composition to have if it was in fact successfully made.

In the instant case, the Collins et al. reference does not show successful recovery of a recombinant RSV having any gene deletion. Moreover, the reference fails to establish that RSV having a partial or complete gene deletion would be expected to possess such critical properties as replication competence, infectivity, immunogenicity, and attenuation *in vivo*. Therefore, the reference fails to provide the requisite "practical motivation" and specific guidance to raise the disclosure beyond what the courts have uniformly characterized as an "obvious to try" teaching—or "an invitation to experiment." As articulated by the District Court in Merck and Co. Inc. v. Danbury Pharacal, Inc., 8 USPQ2d 1793, 1816 (D. Del. 1988) (quoting and citing, respectively, In re Fine, 5 USPQ2d 1596, 1599, (Fed. Cir. 1988), and In re Merck, 231 USPQ 375, 379-80 (Fed. Cir. 1986)):

> [T]he governing standard is emphatically not whether a particular method or process leading to an invention would be "obvious to try", but whether such an experiment would have been expected to succeed.

The Collins et al. reference clearly reflects an "obvious to try" disclosure when viewed in accordance with this legal authority. In particular, Collins and coworkers expressly qualify the limitations of their report, in the very portion relied upon by the Examiner, as follows:

> The ability to introduce defined mutations into infectious RSV should have many applications in extending analyses of RSV molecular biology and pathogenesis. For example, the functions of the RSV proteins, especially the NS1, NS2, SH, M2(ORF1), and M2(ORF2) proteins, could be investigated by introducing mutations that ablate or reduce their level of expression or that yield mutant protein. (p. 11156, left column last paragraph, bridging to right column, emphasis supplied).

In other passages, Collins and coworkers further clarify the hypothetical nature of their discussion, as follows:

> An exciting possibility is that RSV might be engineered in ways that enhance its immunogenicity and induce a level of

> protection greater than that provided by natural infection." (page 11167, left column, last paragraph).
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> ***
>
> Also, it should be possible to explore other methods of attenuation. (page 11165, right column, last partial paragraph).

These collective expressions--"should have many applications", "could be investigated", "exciting possibility", "might be engineered", and "should be possible to explore"--clearly indicate that the Collins et al. report provides no more than an invitation to experiment. It therefore cannot be fairly concluded on the present record that a skilled artisans would have viewed the Collins disclosure as providing a "reasonable expectation of success" for making a recombinant RSV gene deletion mutant that would retain, or acquire, the particular characteristics described by Applicants.

Only with the benefit of hindsight based on Applicants' detailed disclosure is it reasonable to predict that a recombinant RSV having a partial or complete gene deletion is recoverable from cDNA as a self-replicating, infectious, immunogenic, and attenuated construct which would be useful within immunogenic compositions as presently claimed. Without the benefit of Applicants' disclosure, Collins et al. simply suggest that defined mutations may be introduced into a recombinant RSV. The reference speculates regarding a large laundry list of possible permutations in recombinant RSV, but notably fails to provide working examples of any actual constructs, nor evidence of their expected viability and immunological characteristics. This factual scenario squarely fits the nonobviousness analysis provided by the Federal Circuit in In re O'Farrell,

> [i]n some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication or which parameters were critical or no direction as to which of many possible choices is likely to be successful." 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

In view of the foregoing evidence and authority, Applicants respectfully request that the rejection of claims 63-67, 89, 93-95, 120, 121, 128, 131-136, and 150 under 35 U.S.C. § 103 over Collins et al. be withdrawn.

Claims 122, 129, and 130 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Collins et al. in view of Randolph et al. (EPA 0 567 100). Collins et al. is relied upon by the Office as set forth above. Randolph et al. is secondarily cited for teaching intranasal administration of an aerosol containing 10^6 PFU of attenuated infectious RSV for eliciting systemic immunity. Combining these alleged teachings, the Office contends that it would have been prima facie obvious to administer the recombinant RSV taught by Collins et al. via the dosage and route taught by Randolph et al.

Applicants respectfully traverse this rejection on the basis that Collins et al. is a defective primary reference and does not disclose or suggest the recombinant RSV as alleged by the Office. The reasons in support of this position are set forth in detail above. Randolph et al. does not cure these deficiencies of Collins et al. For these reasons, the proposed combination of the RSV vaccine as allegedly taught by Collins et al. with a delivery mode as allegedly taught by Randolph et al. is not supported. Withdrawal of the rejection of claims 122, 129, and 130 under 35 U.S.C. 103(a) is therefore earnestly solicited.

Claim 160 is rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Collins et al. in view of Klein et al. (WO 93/14207). Collins et al. is relied upon by the Office as set forth above. Klein et al. is secondarily cited for teaching "multimeric hybrid genes" comprising gene sequences from RSV and PIV, and that recombinant antigens encoded by such hybrid genes are capable of protecting infants and other susceptible individuals against both RSV and PIV. On this basis, the Office contends that it would have been obvious to incorporate a PIV gene or gene segment into an infectious recombinant RSV as allegedly taught by Collins et al. to elicit an immunogenic response against both pathogens by administration of a single virus.

Applicants respectfully traverse this rejection on the basis that Collins et al. is a defective primary reference and does not disclose the recombinant RSV as alleged by the Office. The reasons in support of this position are set forth in detail above. Klein et al. does not cure these deficiencies of Collins et al. For these reasons, the proposed combination of the RSV vaccine as allegedly taught by Collins et al. with a multivalent vaccine construction as allegedly taught by Klein et al. is not supported. Withdrawal of

the rejection of claim 160 under 35 U.S.C. 103(a) is therefore respectfully requested.

Patentability Under 35 U.S.C. § 112, Second Paragraph

Claim 120 is rejected under 35 U.S.C. 112, second paragraph, for allegedly being indefinite. The Office is correct in noting that the term "complete virus" does not apply to recombinant RSV of the presently elected invention "comprising a partial or complete gene deletion." The term instead applies to non-elected subject matter (e.g., to complete, recombinant RSV, including for example RSV engineered to have partial or complete gene substitutions, gene rearrangements, modifications such as gene "knock outs" that alter or ablate gene expression without deleting all or part of the subject gene, and the like). The amendment herein, canceling claim 120 without prejudice, accords with the Office's understanding and obviates the rejection of claim 120 under 35 U.S.C. 112, second paragraph.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 425-455-5575.

Respectfully submitted,

Date: 4/7/03

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

SHOWN BELOW ARE ALL PENDING CLAIMS CURRENTLY UNDER EXAMINATION (EXCLUDES WITHDRAWN CLAIMS DIRECTED TO NON-ELECTED INVENTIONS, AND WITHDRAWN CLAIMS DIRECTED TO NON-ELECTED SPECIES WITHIN THE ELECTED GROUP)

63. An isolated infectious recombinant respiratory syncytial virus (RSV) comprising a RSV genome or antigenome, a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase protein (L), and a RNA polymerase elongation factor, wherein a modification is introduced within the genome or antigenome comprising a partial or complete gene deletion, a change in gene position, or one or more nucleotide change(s) that modulate expression of a selected gene.

64. The recombinant RSV of claim 63, wherein said gene is selected from an attachment (G) protein, fusion (F) protein, small hydrophobic (SH) protein, RNA binding protein (N), phosphoprotein (P), large polymerase protein (L), M2(ORF1) or M2(ORF2) product, matrix (M) protein, or a nonstructural protein NS1 or NS2.

65. The recombinant RSV of claim 63, wherein a RSV gene is deleted in whole or in part.

66. The recombinant RSV of claim 65, wherein a SH, NS 1, NS2, or G gene is deleted in whole or in part.

67. The recombinant RSV of claim 66, wherein the SH gene is deleted.

89. The recombinant RSV of claim 63, wherein the genome or antigenome is further modified to incorporate one or more attenuating mutation(s) present in one or more biologically derived mutant human RSV strain(s).

93. The recombinant RSV of claim 89, wherein the genome or antigenome incorporates at least two attenuating mutations.

94. The RSV of claim 1, having at least three attenuating mutations.

95. The recombinant RSV of claim 89, wherein the genome or antigenome includes at least one attenuating mutation stabilized by multiple nucleotide changes in a codon specifying the mutation.

121. The recombinant RSV of claim 63 which is a subviral particle.

122. (Amended) The recombinant RSV of claim 63, formulated in a dose of [103 to 106 PFU] 10^3 to 10^6 PFU of attenuated virus.

128. (Amended) [A vaccine to induce protection] An immunogenic composition effective to elicit an immune response in a mammalian subject directed against RSV, which comprises an immunologically sufficient amount of the recombinant RSV of claim 63 in a physiologically acceptable carrier.

129. (Amended) The [vaccine] immunogenic composition of claim 128, formulated in a dose of [103 to 106 PFU] 10^3 to 10^6 PFU of the attenuated RSV.

130. (Amended) The [vaccine] immunogenic composition of claim 128, formulated for administration to the upper respiratory tract by spray, droplet or aerosol.

131. (Amended) The [vaccine] immunogenic composition of claim 128, wherein the recombinant RSV elicits an immune response against human RSV A, human RSV B, or both.

132. An expression vector comprising an isolated polynucleotide molecule encoding a respiratory syncytial virus (RSV) genome or antigenome modified by a partial or complete gene deletion, a change in gene position, or one or more nucleotide change(s) that modulate expression of a selected gene.

133. An isolated polynucleotide molecule comprising a respiratory syncytial virus (RSV) genome or antigenome which is modified by a partial or complete gene deletion, a change in gene position, or one or more nucleotide change(s) that modulate expression of a selected gene.

134. The isolated polynucleotide molecule of claim 133, wherein a RSV gene is deleted in whole or in part.

135. The isolated polynucleotide molecule of claim 134, wherein a SH, NS 1, NS2, or G gene is deleted in whole or in part.

136. The isolated polynucleotide molecule of claim 135, wherein the SH gene is deleted.

148. The isolated polynucleotide molecule of claim 133, wherein the genome or antigenome is further modified to incorporate one or more attenuating mutation(s) present in one or more biologically derived mutant human RSV strain(s).

150. The isolated polynucleotide molecule of claim 148, wherein the genome or antigenome incorporates at least two attenuating mutations.

160. The isolated polynucleotide molecule of claim 133, wherein the genome or antigenome incorporates a heterologous gene or genome segment from parainfluenza virus (PIV).